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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/00 | A2

(11) International Publication Number: WO 00/33812

(43) International Publication Date: 15 June 2000 (15.06.00)

(21) International Application Number: PCT/US99/28697

(22) International Filing Date: 7 December 1999 (07.12.99)

(30) Priority Data:
60/111,285 7 December 1998 (07.12.98) US

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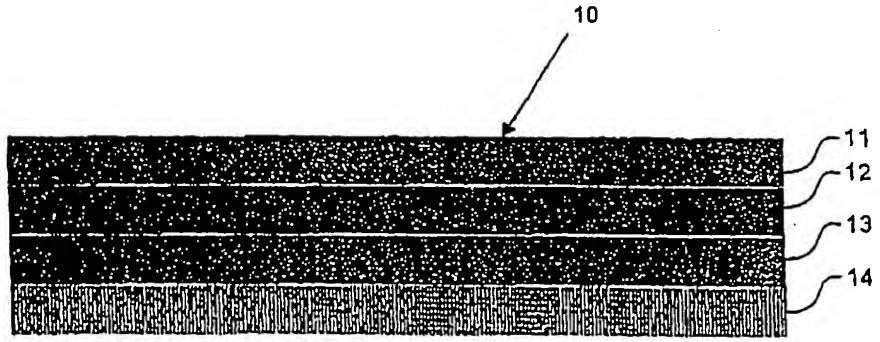
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS



(57) Abstract

A transdermal patch for administering a volatile liquid drug, such as nicotine, transdermally to a patient comprising a four-layer laminated composite of: a top drug impermeable backing layer; a pressure sensitive silicone adhesive layer containing the drug; a pressure sensitive acrylic adhesive layer also containing the drug; and a removable siliconized release liner layer. Also disclosed is a method for treating a person for nicotine dependence and particularly for treating a woman for nicotine dependence.

TRANSDERMAL PATCH FOR DELIVERING VOLATILE LIQUID DRUGS

TECHNICAL FIELD

This invention is in the field of transdermal drug delivery devices. More particularly, it relates to a method for making transdermal patches that deliver volatile liquid drugs, such as nicotine, mecamylamine and selegiline, and to the resulting patches. The invention also relates to a method for treating a person for nicotine dependence comprising transdermally administering an effective amount of mecamylamine to the person without transdermal coadministration of nicotine. The invention further relates to a method for treating women for nicotine dependence comprising transdermally co-administering effective doses of mecamylamine and nicotine.

BACKGROUND ART

There are two basic types of transdermal patches that are used to deliver liquid drugs. One is a liquid reservoir patch in which the liquid drug, either neat or dissolved in a carrier, is confined in a pouch or sac within the device. An example of such a device for delivering nicotine is shown in Fig. 1 of U.S. Pat. No. 5,364,630. The other is a matrix patch in which the liquid drug is dissolved in one or more polymeric layers of a laminated composite. Examples of matrix patches that deliver nicotine are described in U.S. Pat. No. 5,603,947. The present invention relates to a matrix patch.

In the manufacture of matrix patches for administering volatile liquid drugs such as nicotine it is common to attempt to avoid steps involving heat treatment, e.g., drying, so as to avoid excessive loss or degradation of the drug. For instance U.S. Pat. No. 4,915,950 and 5,603,947 describe a printing procedure whereby neat nicotine is applied to a nonwoven fabric laminated to a polyisobutylene adhesive layer. Alternatively "hot" melt adhesives that melt at relatively low temperatures have been used as a matrix material for these drugs. See U.S. Pat. No. 5,411,739.

PCT Pub. No. WO 96/40085 describes transdermal matrix patches for administering drugs such as selegiline. nitroglycerin and nicotine, that are liquid at normal room temperature. The publication suggests making a monolithic matrix of the drug in an adhesive by mixing one

or more polymeric adhesives, preferably polyacrylate and polysiloxane, and the drug in a volatile solvent, casting the mixture, and evaporating the solvent. The publication lists as examples of volatile solvents isopropanol, ethanol, xylene, toluene, hexane, cyclohexane, heptane, ethyl acetate and butyl acetate.

When silicone adhesives have been used as the matrix material in nicotine patches the matrix layer has been cast from a heptane solution. See, for instance, Example 1 of U.S. Pat. No. 5,603,947. Other co-solvents, including hexane, have been suggested for use with silicone adhesives used in transdermal devices. See p. 3, line 51, et seq. of EPO 524776 A1.

Mecamylamine is an antagonist to nicotine. U.S. Patent Nos. 5,316,759, 5,726,190, and 5,574,052 teach the coadministration of mecamylamine and nicotine to treat nicotine dependency. These patents do not teach or suggest the transdermal administration of mecamylamine itself to treat nicotine dependency. Furthermore, the prior art does not teach that coadministration of mecamylamine and nicotine is especially effective as a smoking cessation aid specifically suited for women.

DISCLOSURE OF THE INVENTION

One aspect of this invention is a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) a top backing layer that is impermeable to the drug;

b) silicone adhesive layer containing the drug and underlying the backing layer;

c) an acrylic adhesive layer also containing the drug that underlies and is in diffusional contact with the silicone adhesive layer; and

d) a removable release liner layer underlying the acrylic adhesive layer, wherein the combined amount of drug in the silicone adhesive layer and the acrylic adhesive layer is sufficient to provide a therapeutically effective amount of drug to the patient.

Another aspect of the invention is a method of making a transdermal patch for administering a volatile liquid drug transdermally to a patient comprising:

a) coating a solution of the drug and a silicone adhesive in hexane onto a backing layer;

b) evaporating the hexane from the coating to form a silicone adhesive layer containing the drug; and

As used herein the term "treating a person for nicotine dependence" intends causing the person to reduce or eliminate his or her intake of nicotine from smoking and/or chewing tobacco on a temporary or permanent basis.

The embodiment of the invention shown in Figure 1 is a four-layer laminated composite matrix type transdermal patch, generally designated 10. The four layers are: (1) a top drug-impermeable backing layer 11; (2) an intermediate drug-containing silicone adhesive layer 12; (3) a basal drug-containing polyacrylic adhesive layer 13; and (4) a removable release liner layer 14.

Materials for making backing layer 11 are well known in the art. They include various polymers such as polyethylene terephthalate, polyethylene, polypropylene and polyvinyl chloride, metal foils such as aluminum foil, and polymer-metal composites.

Adhesive layer 12 is made from a pressure sensitive silicone adhesive. An amine compatible silicone adhesive is preferred for use with drugs, such as nicotine, which contain amine groups. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989). See also Pfister, W.R., et al. "Silicon Adhesives for Transdermal Drug Delivery" Chemistry in Britain (Jan. 1991), pp. 43-46 and EP Pub. No. 0524776 A1. Suitable commercially available silicone pressure sensitive adhesives are available from Dow Corning under the trademark BIO-PSA. The silicone pressure sensitive adhesives are supplied commercially as solutions in a solvent. Per the present invention the solvent should be hexane. The thickness of layer 12 will usually be in the range of about 25 to 100 microns, more usually 50 to 75 microns. Expressed alternatively, the layer 12 will be present at about 4 to 18 mg/cm^2, more usually 8 to 14 mg/cm^2. Adhesive layer 12 initially (before it is laminated to adhesive layer 13) contains the entire drug loading. In this regard, the drug(s) will usually be added to the silicone adhesive in amounts ranging between about 5% to 50% by weight, more usually 10% to 30% by weight, based on the total dry weight of drug and adhesive.

Adhesive layer 13 is made from one or more solution acrylic pressure sensitive adhesives. These adhesives are described in detail in the Handbook of Pressure Sensitive Adhesive Technology, 2nd Edition, pp. 396-456 (D. Satas, ed.) Van Nostrand Reinhold, New

York (1989). They are usually copolymers composed of: 50% to 90% of a main acrylate or methacrylate monomer, usually 2-ethylhexyl acrylate, butylacrylate, or iso-octyl acrylate; 10% to 40% of a modifying monomer such as vinyl acetate; and 2% to 20% of a functional group-containing monomer such as acrylic acid. Examples of suitable commercially available solution acrylic pressure sensitive adhesives are: National Starch DuroTak® adhesives 87-2194 and 87-2070. The thickness of the acrylic adhesive layer 13 will usually be about the same as that of layer 12. After lamination to the silicone adhesive layer 12 and equilibration of the drug between layers 12 and 13, layer 13 will also contain drug. In this regard the drug will usually constitute about 2.5% to 30% by weight, preferably 5% to 15% by weight, of layer 13 after equilibration occurs.

The release liner layer 14 is removed before device 10 is placed on the skin. After layer 14 is removed the lower surface of layer 13 is exposed and defines the basal surface of the device which is intended to be placed directly in contact with the skin. Release liner layers are well known in the transdermal patch art. They are made of materials that permit the layer to be easily stripped or peeled away from the adjacent pressure sensitive adhesive layer. Release liner layers are typically made from drug impermeable polymers such as polyesters which are coated with materials such as silicone or fluorinated hydrocarbons that reduce the adhesiveness between it and the adjacent pressure sensitive adhesive layer. In this regard since the acrylic pressure sensitive adhesive layer rather than the silicone pressure sensitive adhesive layer defines the basal surface of the device it is possible to use a siliconized release liner. Such liners are generally not compatible with silicone adhesives. Siliconized liners are more economical than fluorocarbon coated liners. Further, use of the acrylic pressure sensitive adhesive as the basal layer provides a more controlled and predetermined delivery of the drug than could be achieved using a silicone adhesive basal layer. The particular drug release profile from the patch can be varied by altering the thickness and/or composition of the acrylic pressure sensitive adhesive layer and/or the drug loading, and/or by employing a permeation enhancer.

The drug is released from the surface of the acrylic pressure sensitive adhesive to the skin at a therapeutically effective rate. That rate will depend upon the particular drug. In the case of nicotine, the rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr. In the case of co-administration of nicotine and the mecamylamine, the nicotine rate will usually be in the range of 0.2 to 1.5 mg/hr, preferably 0.3 to 0.9 mg/hr, and the mecamylamine rate will usually be in the range of 0.02 to 1 mg/hr, preferably 0.1 to 0.6 mg/hr. In the case of

The dried silicone adhesive/nicotine-coated backing layer subassembly was then laminated to the dried acrylic adhesive-coated release liner subassembly to form a four-layer laminated composite. Following lamination, the nicotine distributes itself (via diffusion) uniformly within the adjacent silicone adhesive layer and acrylic adhesive layer of the composite. The concentration of nicotine within the layers was about 6% (w/w) after equilibration.

In vitro nicotine flux from the laminated composite was determined at 32°C through human cadaver epidermis into an infinite sink using modified Franz glass diffusion cells. Nicotine assays were made by HPLC.

For comparison purposes the flux of nicotine from commercial Habitrol3 21 mg/day patches was determined using the same test procedure. Figure 2 is a graph of the nicotine flux from the composite of the example and from the Habitrol3 patches versus time.

Example 2: Preparation and Testing of Nicotine/Mecamylamine Patches

Nicotine and mecamylamine were added to a hexane solution of Dow Corning BIO-PSA amine compatible silicone pressure sensitive adhesive. Two batches were made: one contained approximately 10% nicotine and 6.4% mecamylamine based on the total dry weight of the adhesive and the two drugs; and a second contained approximately 10% nicotine and 4.2% mecamylamine, based on the total dry weight of the adhesive and the two drugs. The batches were separately coated onto a 3M Scotchpak 1109 polyester/polyoefin backing film at 9.6 mg/cm^2 (0.96 mg/cm^2 nicotine, 0.61 mg/cm^2 mecamylamine, 8.03 mg/cm^2 adhesive for the first batch; 0.96 mg/cm^2 nicotine, 0.40 mg/cm^2 mecamylamine, 8.24 mg/cm^2 adhesive for the second batch) and then dried at 30 to 40°C for about 2 min.

A blend of two National Starch DuroTak acrylic solution polymers, 87-2196 and 87-2516, 25% and 75% w/w, respectively, was made. The blend was coated at 8.0 mg/cm^2 onto a 75 micron thick Daubert Coater Products siliconized polyester release liner (1-3 PESTR (Matte) - 164Z) and dried at about 100°C for about 10 min.

The drug-containing silicone adhesive/backing subassembly was then laminated to the acrylic adhesive/release liner subassembly to form a four layer/laminated composite. After lamination the nicotine and mecamylamine distributed themselves uniformly within the adjacent